tissue analysis for gene expression, neuroimaging, pharmacologic intervention and behavioural assessments (such as intruder challenge and novelty response tests), analyzing the data together and interpreting the results as a whole, it will enable a more complete understanding of the processes of brain behaviour.

For Freimer's own research interests, the study specifically provides the necessary information that enables him to better understand brain structures – their size and shape. It is well known that these structures are highly heritable, but it remains to be seen which genes are responsible. It is hoped that collating the data from the colony will make it possible to identify the loci responsible for the variability. From identifying the genes that have a role in a whole range of behavioural traits, the ultimate aim is to ascertain whether these are comparable to genes in humans and whether they function in a similar manner in human brain processes.

Robin Ganellin gives his views on medicinal chemistry and drug discovery

Interview by Stephen L. Carney

C. Robin Ganellin, FRS, Smith Kline & French Professor of Medicinal Chemistry, University College London

Robin Ganellin was born in East London and studied chemistry at Queen Mary College, London, receiving a PhD in 1958 under Professor Michael Dewar for his research on tropylium chemistry. He joined Smith Kline & French Laboratories (SK&F) in the UK in 1958 and was one of the co-inventors of the revolutionary drug cimetidine (Tagamet®) He subsequently became Vice-President for Research at the company's Welwyn facility. In 1986 he was awarded a DSc from London University for his work on the medicinal chemistry of drugs acting at histamine receptors and was also made a Fellow of the Royal Society and appointed to the SK&F Chair of Medicinal Chemistry at University College London, where he is now Emeritus Professor of Medicinal Chemistry. Professor Ganellin has been honoured extensively, including such awards as the Royal Society of Chemistry Award for Medicinal Chemistry, their Tilden Medal and Lectureship and their Adrien Albert Medal and Lectureship, Le Prix Charles Mentzer de France, the ACS Division of Medicinal Chemistry Award, the Society of Chemical Industry Messel Medal and the Society for Drug Research Award for Drug Discovery. He is a past Chairman of the Society for Drug Research, was President of the Medicinal Chemistry Section of IUPAC, and is currently Chairman of the IUPAC Subcommittee on Medicinal Chemistry and Drug Development.

What factors influenced you to begin a career in chemistry?

I suppose it goes back to one's education system and how one reacts to it. At school I found my abilities were skewed very much towards the sciences. I came pretty close to the top in biology and maths and down at the bottom of the class in history and languages. My father and one of my mother's brothers were chemists so you could say there was a genetic determinant. Actually I was very keen on biology and natural history was a sort of hobby for me. I suppose if I was totally free I would have gone on to be a biologist but at the time I felt I didn't know how I would earn my living as a biologist – I didn't know any biologists, but I knew chemists so I went into chemistry.

What aspects of your career have given you most pride professionally and personally?

I find that making discoveries is very exciting; it is the most stimulating part, and especially succeeding where you think others may have failed and doing something really new. I saw this during my PhD studies, when I discovered, partly through chance and partly through reading, that just by treating cyclooctatetraene (an eight-membered hydrocarbon ring) with potassium permanganate solution I could isolate the tropylium cation (which is a seven-membered ring). So you go from C8 to C7 in what apparently was one step. Then I worked out the mechanism and found that incredibly exciting, especially knowing that during the second World War, a famous German chemist called Walter Reppe had been making cyclooctatetraene and then studying its reactions. He had suggested most improbable mechanisms and this little thing we had discovered led to a clear understanding of what those mechanisms must have been. I find it remarkable that our education system can take, in my case, a schoolboy and in a few years produce someone capable of making what I thought were important discoveries.

You asked me, in terms of my career, what has given me most professional pride; that has to be Tagamet®, which was a fantastic achievement. I think that I was very fortunate that things worked out, and it was very difficult to accomplish. I remember after it had come on to the market, going to a family occasion and one of my uncles coming up and saying, thank you. I said 'thank me for what?' and he replied 'for what you have done for me. I've been in bed for two weeks in terrible pain with an ulcer and I've taken this medicine and here

1359-6446/04/$ – see front matter PII: S1359-6446(03)02999-4

I am – feeling wonderful.' That is a hell of a rewarding feeling when you have made something that has become a medicine and people turn round and thank you for doing it. When you talk about professional reward, the people aspect is really something.

'…I think that the application of physical organic chemical approaches to structure–activity analysis have been very important.'

Has there been a single development that, in your opinion, has moved the field of medicinal chemistry ahead more than any other?

I would go back to the 1960s to the work of Corwin Hansch on the importance of lipophilicity. He used octanol:water as a means of partition and replaced what many people had used before, olive oil and things like that. He introduced to medicinal chemists the idea of multiparameter correlation analysis. One could look at a molecule and consider what substituents or groups you are putting in and how they might change the chemistry, and then relate that to the change in biology. Up until then, many people had just produced tables of structures and biological activities and it was just a catalogue. Here was the opportunity to analyze what the catalogue might mean. Some years ago I remember that as you go up a series of alkyl homologues you go from methyl, ethyl, propyl, butyl to futile. Hansch put a cap on this – he showed that it might or might not be futile, depending upon the importance of the contribution of the substituent to lipophilicity. I think that changed the way of thinking in medicinal chemistry. Not everybody took it up immediately but I think that the application of physical organic chemical approaches to structure–activity analysis have been very important. The ability to set up computers to do this for you and also predict what the contribution of lipophilicity might be in a molecule helps a lot of people who might otherwise not have bothered. A lot of information is lying in the literature if you know, first of all, to ask the question and secondly, how to look up the information. Now it is all in programs and ready to hand. So what was once a very slow transformation in the 60s and 70s has now become easy and commonplace because of the availability of desktop computing.

In view of the increase in the number of biologicals entering the market, what do you see as the future for medicinal chemistry within academia and the pharmaceutical industry?

It is interesting you should ask that because just before I left SK & F (in 1986), we went through a very bad period. The senior research people in the United States were keen on molecular biology and they thought the future of the drug discovery industry would be there. So they were of the opinion that they really didn't need so many medicinal chemists in discovery research anymore and we went through a black period within the company. But, of course, the pendulum swung back. Biologicals at that time (and there are still not so many on the market) didn't really look so promising and the immediate prospects were small molecules that had been produced by medicinal chemists. They still represent the main products coming out of the pipeline for major companies. The whole field is expanding and I don't necessarily think that a reduction in the number of chemists will be needed. Chemists have become more effective in the sense that they can now produce many more molecules than they used to. In the first half of the 20th Century the Pharmaceutical industry was really dominated by chemists; biology was mostly very empirical. Now there is a terrific amount of information being generated both in biochemistry and cell biology and I think the industry is largely biologically driven. I would think that the future will lie more with medical people who can identify the medical problem and then help to identify the mechanism, followed by an assay, and then apply chemistry to provide the required drug. I think there are still many opportunities for chemistry and chemists.

'Chemists have become more effective in the sense that they can now produce many more molecules than they used to.'

How has the teaching of chemistry changed in the last ten years to better prepare students for the rapidly changing world of drug discovery?

In chemistry courses throughout the country, there is a greater awareness of what is going on in pharmaceuticals. This is mainly driven by the possibility of getting grants that have identified this as being important. I remember when I was a PhD student, the general view in academia was that industry research was held in pretty low regard. Subsequently, industry has become much more sophisticated and has really shown what it can do, especially when it comes to drug discovery. Universities now sit up and take notice and so in that sense, there has been a big change. Students have also tended to show a greater interest in a subject if they think that it can be applied to solve medical problems. They really like to think that what they are doing is going to make a contribution towards treating people. So this has led many universities to set up a course that includes half a unit on drug synthesis or something about drugs and call it Medicinal Chemistry. Mostly it's not teaching people to become medicinal chemists, it's teaching about some chemical aspects of drugs. There have been very few chemistry departments in the UK that have introduced courses that lead to a degree in Medicinal Chemistry. One is Loughborough University and we do this at University College, London. We began this over 25 years ago through Sir James Black when he joined the Pharmacology department, as Professor of Pharmacology. I am also involved in IUPAC (the International Union of Pure and Applied Chemistry) where there is a medicinal chemistry sub-committee. One of the questions that we discussed was what happens about training medicinal chemists for the pharmaceutical industry? So we sent out a questionnaire to the major pharmaceutical companies, asking them what sort of training they wanted to see. We got an overwhelming return, over 90%, saying that what they really wanted were good synthetic organic chemists and that they themselves would teach the medicinal chemistry. In other words, never mind about the medicinal chemistry, just give us good chemists. We were very surprised about that, and then later I realised that we had biased the results by sending the questionnaire to very big companies, because the very big companies structure themselves so that they have expertise in every area they need. They have very good resident medicinal chemists who can mentor those who come in and do the structure–activity analysis that is required. So their great need is for people who are technically able

to make molecules, which is something that is very hard to do if you don't learn it pretty early on, when you are in your undergraduate and PhD days. Subsequently, when I talked to smaller companies, particularly biotech companies, they were very short of medicinal chemists and always on the lookout for them because they need somebody who has this understanding to help them approach the chemistry in an appropriate way. So there is a different need there. Who fulfils that training is a very interesting question. The schools of pharmacy, particularly in this country, have medicinal chemistry to a greater or lesser degree within them. They don't necessarily teach a sufficiently wide background in chemistry in their courses, and the students obviously have to learn very many things to do with pharmacy. So on the one hand, they are training people who are more generalists, and on the other hand you have the chemistry departments who are training people as specialist chemists with not much biology. What we were doing at University College was giving people a course in which they had most of the chemistry, but also biochemistry, physiology and pharmacology. They took pharmacology every year, so they come out having a good understanding of pharmacology – they didn't come out as pharmacologists, of course.

'This desire to play safe, I think, kills research…'

What is your view on the trend for merging and/or acquiring pharmaceutical companies? Do you think this will help or hinder the production of blockbuster drugs?

Seeing four major research groups in this country, Smith Kline, Glaxo, Wellcome and Beecham merge and those four separate identities disappear, has I think been absolutely tragic for research in the UK, but I suppose it is a natural part of life. We have seen it happen in the past century with the car industry and in pharmaceuticals there has always been some merging. SK & F had its mergers and Merck merged with Sharp and Dohme in the 60s, and so on. The rate has increased greatly and the companies have become extremely large. One of the problems with it is that they are so aware of their size that they lose the opportunity to take chances. This desire to play safe, I think, kills research in the sense that you need to be prepared to take risks in research. You take risks all the way through; you take risks as to whether or not the program is going to work, whether you are going to make a successful compound, whether it is going to work the right way in human studies, and so on. I think this gives the big companies clay feet. What we have seen happen is that the big risk takers are the biotech companies and when they have found something they run on venture capital, which is risky capital, everybody knows that. The venture capitalists take a bit of their portfolio and put it into a big risk and expect to lose nine-tenths of it, but the tenth that wins might actually produce a terrific return for them. We can see this happening now. Companies start up, they last three or four years while they take their idea or invention through, then they fail and it doesn't hurt, except with regards to the capital that was originally invested. So the long-term investor is not affected, whereas the larger companies cannot afford to take that chance anymore – they are looking over their shoulder at the investor market all the time. When a biotech company is successful, it has to grow and either it does so with more capital or a big company acquires it. That appears to be a rather interesting fractionation of risk within the industry.

'Seeing four major research groups in this country…merge and those four separate identities disappear, has I think been absolutely tragic for research in the UK.'

How do you view the interaction between industry and academic chemistry departments? Does it allow for an appropriate level of speculative research, or is it too restrictive?

There is big pressure on universities now to go into areas that are determined politically by the funding councils and I think this is very bad for discovery. There is too much pressure to go into applied areas. One should allow people a lot more freedom to speculate and make their own discoveries. For that, you need to remove some of the pressure that is on people. I worry about the future of research in this country because, looking at my colleagues, I have been appalled at the extent to which they have to spend their time either teaching, writing grants or attending administrative meetings. They don't have nearly as much time for research as they used to. This is because everything has been pared down so that there are fewer people – the technical help has been cut away and everybody is doing their own thing. Almost all the secretaries have gone, because everybody has got their own computer. Well this is all right, but you are not allowing the people to spend their full time on research and I think that is very bad and not at all cost-effective. The government is encouraging research to be self-funding and it is doing the same with teaching and the question of top-up fees, and so it is saying 'you should be going out and getting money for it yourself'. The previous governments withdrew a lot of funding from the universities and a lot of the fabric of the university has just been crumbling. To start with, you cut off a bit of fat and you make them leaner and apparently more productive, but in the end, I think we have reached a situation of diminishing returns because of this attitude. Part of the attitude of the politicians appears to be 'well you universities, you are making all these discoveries, but you haven't been applying them – you should get involved with industry more'. I don't think it is the problem of the universities, I think it is really a problem with the investors and it has been far too easy in this country for investors to make money by just investing in property and they don't seem to be interested in investing in technical invention at all. Every time I talk to people who have been trying to raise capital for whatever they are doing, they tell me that they are going to the United States. They can't get capital in this country – it is not a question of academics approaching industry, it is more a question of where there is capital and why it is not being invested into technology. That question doesn't seem to get asked over here.

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